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Iminoether - Enaminoether Tautomerism. Elaboration of Quaternary Carbon Centers by a New Michael-type Reaction

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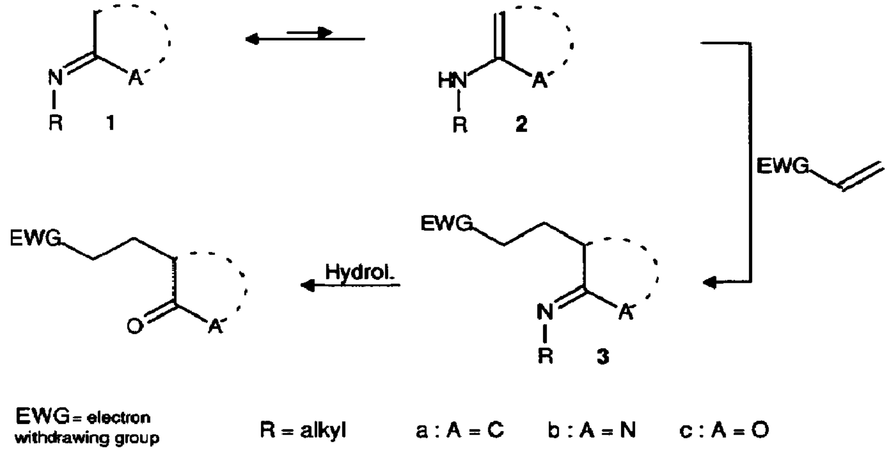
Abstract *. Cyclic iminoethers 4 and 10 have been shown to be in N,C-tautomeric equilibrium with their corresponding secondary enaminoethers 5 and 11 which can be C-alkylated with electrophilic olefins leading to functionalized α,α-disubstituted iminoethers 8 and 12 and yielding the corresponding lactones 9 and 13 upon hydrolysis.*

Michael addition of imines **1a**, reacting as their secondary enamine tautomers **2a**, has been studied with acyclic and cyclic imines[1] and, in the second case, has been extended to a new type of asymmetric synthesis[2] involving many useful applications[3] (Scheme 1).



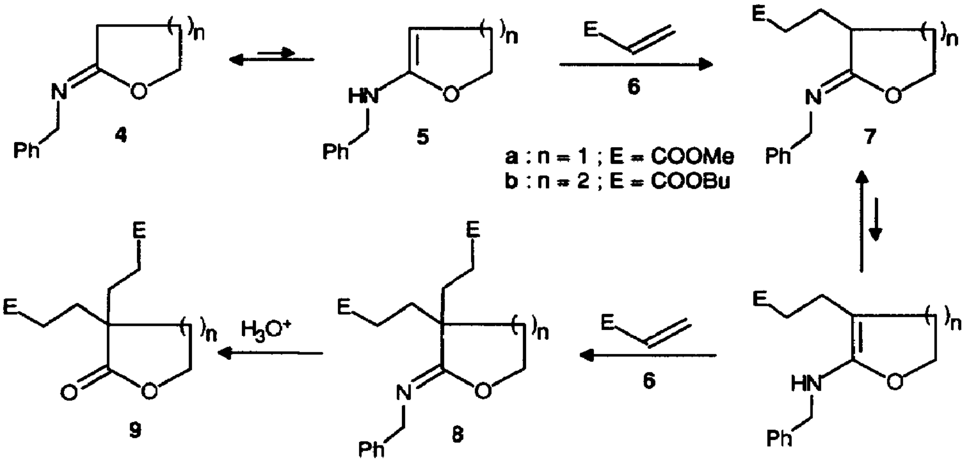
Scheme 1

A similar Michael reaction taking place with amidines **1b** reacting as their ene-1,1-diamines tautomers **2b**, was recently described[4].

In this Letter we report results dealing with cyclic iminoethers **1c** which show that in this instance too, Michael reactions do occur.

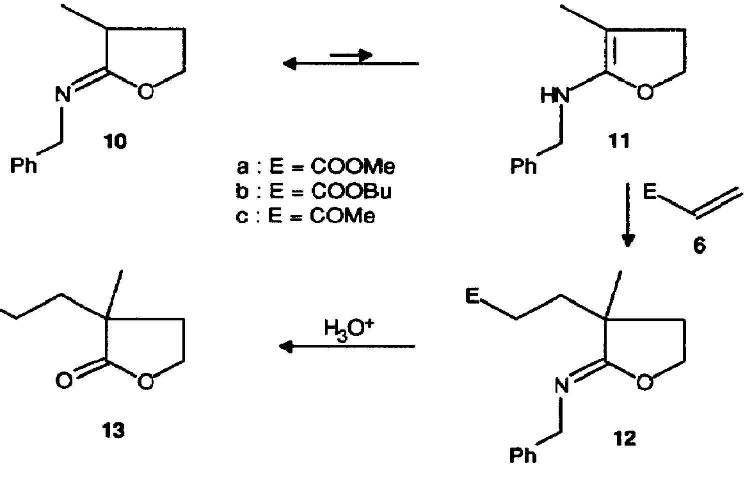
Cyclic iminoethers **4a**, **4b** and **10** were prepared from the corresponding lactones and benzylamine, according to a method described previously[5].

The existence of the equilibrium **4a** $\rightleftharpoons$ **5a** (Scheme 2), at least in methanolic medium, is demonstrated by the same method which was used before to prove the existence of imine-secondary enamine[1a,b] and amidine-enediamine[4] tautomerism, *i.e.* by ^{1}H NMR of a CD_3OD solution of iminoether **4**[6].



Scheme 2

After 23 hours at room temperature there is a complete disappearance of the triplet signal (2.75 ppm) corresponding to the two hydrogen atoms in the α-position relative to C=N ($\tau_{1/2}$ = 5 h). With iminoether **10** (Scheme 3) the α-hydrogen atom (t of q, 2.95 ppm) has $\tau_{1/2}$ = 3 h.



Scheme 3

These experiments show that tautomerism occurs, although at equilibrium (as in the case for secondary enamines[1a,b] and ene-1,1-diamines[4]), the enaminoether forms **5** and **11** should be present at less than 3% since no vinyl hydrogen or vinyl methyl can be detected in the ^{1}H NMR spectra of iminoethers **4** and **10** in $CDCl_3$.

A literature survey has not revealed any reactions occurring between iminoethers of type **4** (or **10**) and electrophilic olefins.

When 5- and 6-membered unsubstituted iminoethers **4a** and **4b** were reacted with three equivalents of acrylic esters **6a**[7] and **6b**, bis-adducts **8a** and **8b** were obtained (Scheme 2 ; Table, entries 1,2). For characterization purposes, the adducts were purified by flash chromatography (FC) and the indicated yields are minimum values since these iminoethers are partially hydrolysed during the process. 10% acetic acid hydrolyses of adducts **8** gave lactones **9** along with opened compounds, the corresponding ω-hydroxy carboxylic acids. The six-membered iminoether **8b** (entry 2) is particularly prone to give this type of hydrolysis, thus lowering the yield of lactone **9b**.

Table. Michael Additions of Cyclic Iminoethers[a]

Entry	Starting iminoether	Electrophile[b]	Temp.(°C)	Time (days)	Iminoether conversion (%)[c]	Adduct	Yield (%)[d,e]	Lactone[f]	Yield (%)
1	**4a**	**6a**	80	13	85	**8a**	87	**9a**	90
2	**4b**	**6b**	140	2	>99	**8b**	70	**9b**	55
3	**10**	**6a**	80	15	>99	**12a**	98	**13a**	85
4	**10**	**6b**	140	0.75	82	**12b**	80	-	-
5	**10**	**6b**	140	1	86	-	-	**13b**[g]	83[d]
6	**10**	**6c**	80	1	89	**12c**	92	-	-
7	**10**	**6c**	80	1	90	-	-	**13c**[g]	93[d]

(a) Reactions were performed under nitrogen at the multi-gram scale and followed by GC/MS. New compounds **8**, **9**, **12** , and **13** were purified by FC (SiO_2 ; AcOEt / hexane eluent) and gave spectra (^{1}H NMR, ^{13}C NMR, IR, MS) in accordance with the structures indicated.

(b) 3 equiv. (entries 1,2), 1.1 equiv. (entries 3-7), with 0.5% equiv. of 4-methoxyphenol ; no solvent.

(c) GC/MS determination (see end of Note 5).

(d) based on converted iminoether.

(e) Minimum values ; see text.

(f) Hydrolyses were performed by adding THF and 1.1 equiv. of 10% AcOH (iminoether *ca.* 0.4 M) followed by heating the solution at 40 °C for 24h.

(g) One-pot synthesis.

Interestingly, from a synthetic point of view, when butyrolactone enolate is reacted with methyl acrylate, compound **9a** cannot be isolated since Dieckmann cyclization occurs, affording instead the corresponding spiranic compound in 50-55% yield[8].

With 2-methyl-substituted iminoether **10** and 1.1 equivalent of acrylic esters **6a** and **6b** (entries 3,4) or methylvinylketone **6c** (entry 6), adducts **12** were obtained and isolated by FC (*vide supra* for yield values).

Hydrolyses gave lactones **13** with small amounts of the corresponding opened compounds (*vide supra*) and can be performed with advantage, on the crude reaction mixtures (entries 5,7).

Compared with imines[1] (the most reactive) and amidines[4], iminoethers display an intermediate reactivity towards electrophilic olefins.

A new tautomeric process has been uncovered with cyclic iminoethers which allows to perform Michael reactions leading to unreported functionalized α,α-disubstituted lactones.

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6. The method has been also applied to demonstrate a related tautomeric equilibrium with lactim-ethers : Granik, V.G.; Pyatin, B.M.; Persianova, J.V ; Peresleni, E.M.; Kostyyuchenko, N.P.; Glushkov, R.G.; Sheinker, Y.N. *Tetrahedron* **1970**, *26*, 4367-4373.

7. When iminoether **4a** was reacted with ¼ equivalent of acrylic ester **6a**, a mixture of mono- and bis-adduct was obtained (with the corresponding amidine[4], the mono-adduct was obtained almost quantitatively in these conditions).

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